REMARKS/ARGUMENTS

The Examiner is thanked for the many helpful explanations and analysis in the most recent office action. The specific remaining rejections are discussed below.

The examiner rejects the claims as overly broad and not enabled under section 112 based on the recitation of "androgens" "estrogens" and "selective estrogen receptor modulators." However, these terms are well-defined in the art, and represent a classes of compounds whose members are expected to behave similarly. The function of androgen and estrogen receptors is well characterized such that all androgens and all estrogens are expected to interchangably have analogous function when acting upon those receptors.

The term "derivative" is alleged by the examiner to be indefinite under section 112. However, the term is well-known to encompass compounds having a particular basic structure in common. For example, "phenylindole derivative" in claim 1 unambiguously covers compounds having a phenylindole moiety within its molecular structure. It is urged that there is no lack of clarity.

For the foregoing reasons, it is urged that the rejections under section 112 be withdrawn.

The claims stand rejected by the examiner as allegedly obvious under section 103 in view of a number of references of record. However, it is believed that a prima facie case of obviousness has not been made for the reasons discussed below.

35 U.S.C. 103 authorizes a rejection where, to meet the claim, it is necessary to modify a single reference or to combine it with one or more other references. After indicating that the rejection is under 35 U.S.C. 103, the examiner should set forth in the Office Action:

(A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate,

(B) the difference or differences in the claim over the applied reference(s),

(C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and

(D) an explanation why one of ordinary skill in the art at the time the invention was made would have been motivated to make the proposed modification.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - §2143.03 for decisions pertinent to each of these criteria.

The examiner's position regarding two of the requirements: (1) the prior art's motivation to combine references and (2) the prior art's expectation of success in the presently-claimed combination, is best summarized at the bottom of page 11 of the office action. It is this summary with which applicant respectfully disagrees. First the examiner speaks broadly of "estrogen sensitive" diseases when there are two important and opposite sub-types of such diseases: (1) those conditions that respond favorably to estrogen (and unfavorably to antiestrogen) and (2) those conditions that respond unfavorably estrogen (and favorably to antiestrogen). One of skill in the art simply would not be motivated to use an estrogenic or antiestrogenic pharmaceutical useful against one sub-group of conditions for treatment of the other sub-group of conditions where the pharmaceutical would be expected to have the opposite (and adverse) effect. The examiner concedes that selective estrogen receptor modulators (SERMs) may have antiestrogenic activity, then concludes that it is predictable whether estrogenic or antiestrogenic effects will be observed when estrogen is combined with SERMs (potential antiestrogens). However, it is only applicant's specification - - and not the prior art - - which teaches what will happen in various tissues once these potentially opposing compounds are simultaneously introduced.

At most, the Examiner's proposed combination of references imposes an improper "obvious to try" standard. But even if it were shown that applicant's procedures were "obvious to try", the references did not show that there was a reasonable expectation of success. This is a requirement of §103 which is not met by the cited references. See Amgen v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 U.S.P.Q. 1016 (Fed. Cir. 1991). In re O'Farrell, 853 F.2d

894, 904-04, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988). Whether a particular combination might be "obvious to try" is not a legitimate test of patentability. In re Fine, 5 U.S.P.Q.2d, 1596, 1599 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 688, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir.1987). The claimed combination cannot be obvious without a suggestion in the art that the references should be combined as the Examiner suggests, and a predictability in the art that the combination would be effective. Because such a suggestion is lacking from the cited art, it is urged that the Examiner's rejection under 35 U.S.C. §103 should be withdrawn.

As discussed in detail below, the present specification sets forth a large amount of highly surprising data showing unexpected and unpredictable advantages from combining SERMs with estrogens. The prior art would more likely have expected redundant or even counterproductive results from the combination. Indeed, because SERMs may act as estrogen antagonists in many tissues, it might have been expected that the advantages afforded by estrogens would have been stopped by SERMs when acting in their capacity as estrogen antagonists.

The unexpected finding of the present invention, as shown in a large amount of data presented in the specification, is that SERMs selectively reverse only the negative effects of estradiol -- not its positive effects. This unexpected advantage is neither disclosed nor suggested in the Examiner's cited art, but is discussed in great detail in the present specification. For example, at page 20, line 21 through page 21 line 3, it is stated that:

> "On the other hand, osteoporosis, hypercholesterolemia, hyperlipidemia, cognition and atherosclerosis respond favorably to estrogenic or estrogen-like activity. By using estrogens in combination with SERMs in accordance with the invention, desirable effects are provided in target tissues without undesirable effects in certain other tissues. For example, the combination of an estrogen and a SERM can have favorable estrogenic effect in the bone (or on lipid or cholesterol) while avoiding unfavorable estrogenic effect in the breast and uterus since the SERMs will, acting as estrogen antagonists, efficiently block the effect of estrogen in the breast and endometrium as seen in figure 10 and 11."

The unexpected synergy provided by the claimed combination is further explained in the final paragraph of page 21:

> "Undesirable effects are also mitigated in a synergistic way by the combination used in the invention. For all diseases discussed herein, any other effect on breast tissues that might otherwise result from estrogens given at a replacement dose is efficiently blocked by the antiestrogenic effect of the SERM in breast tissue as seen in Figure 2 and 3. The same conclusion can be reached from Fig. 10."

The carryover paragraph on pages 22-23 of the application further explains that estrogens, which can pass through the brain barrier to restore normal estrogenic action there, are not antagonized in the brain by preferred SERMs of the invention, because the brain barrier, as shown in example 9 is a significant barrier to the SERM. Thus, the positive effects of estrogen in the brain are not antagonized even while the SERMs effectively antagonize the negative effects of estrogen in the breast, uterine and endotremial tissues.

Example 5 and Tables 6 and 7 show that, at the concentration used, the administration of the SERM, EM-652.HCl, does not counteract the beneficial effect of estrogen on cholesterol. Yet, Example 10 shows that the combination of the antiestrogen EM-652.HCl with the estrogen estradiol protects against uterine stimulation in female rats. See page 95, lines 9-20, where it is stated that:

> "A 37% increase in serum cholesterol was observed 2 weeks after OVX ($p < 0.01$). Treatment of OVX animals with E_2, on the other hand, caused a 53% ($p < 0.01$) inhibition of serum cholesterol levels (Fig. 25). The addition of EM-652.HCl at the daily doses of 0.01 mg/kg to 0.3 mg/kg had no statistically significant effect on the inhibitory action of E_2. On the other hand, the 1.0, 3.0 and 10 mg/kg doses of EM-652.HCl reduced by 36%, 30% and 50%, respectively, the effect of E_2."

It is important to note that the daily dose of 0.3 mg/kg seems to be the best one. In fact, this dose does not negatively affect the cholesterol levels as shown in figure 25 but reverses by more than 61% and 54% the undesirable estradiol-induced increases in uterine weight (Figure 21) and

endometrial epithelium height (Figure 22), respectively. However, the doses must be adjusted for each individual patient. For example, for a person having a high risk of breast cancer, higher doses of the antiestrogen EM-652.HCl can be used. This is clearly demonstrated in the example 10 (Figures 21-25) where it can also be seen that higher doses of EM-652.HCl (1.0, 3.0 and 10 mg/kg) cause a more complete reversal of the undesirable effects due to estradiol.

For all of the foregoing reasons, it is believed that the combination of SERM and estrogen, which is not even discussed in the cited prior art, produces numerous advantageous and unexpected effects which are neither disclosed nor suggested by the prior art. Accordingly, it is urged that the Examiner's art rejection should be withdrawn.

Regarding the double patenting rejection over (A) U.S. patent 6,670,346 and (B) U.S. patent 6,465,445, it is noted that the cited patents require a sex steroid precursor such as DHEA, while the present claims require estrogen. The physiological effects of these two compounds differ, and the examiner has not shown why it would be considered obvious to substitute one for the other.

Regarding the double patenting rejection over copending patent application serial number 10/143894, the examiner is referred to the enclosed excerpt from a restriction requirement issued in application 09/771,180, the parent application to both the present application and the reference application. In that restriction, the U.S. Patent Office determined that menopause claims were patentably distinct from other method claims similar to those pending in the reference. It would not be proper to now reject, for double patenting, subject matter previously adjudged patentably distinct.

For all of the foregoing reasons, it is urged that the application is now in condition for allowance. Issuance of a notice of allowance is solicited.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on April 18, 2005:

William O. Gray, III
Name of applicant, assignee or Registered Representative

Signature

April 18, 2005
Date of Signature

WOG:db

Respectfully submitted,

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Office Action Summary	Application No.	Applicant(s)	
	09/771,180	LABRIE, FERNAND	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-37* are subject to restriction and/or election requirement.

EXCERPTS FROM PARENT, Office Action

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application claims priority to provisional application Serial No. 60/178,601.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 8, and 12-37 drawn to a method of reducing or eliminating the incidence of menopausal symptoms, classified in class 514, subclass 169 for example.

II. Claims 2-3, 7, and 9 drawn to a method of treating or reducing the risk a condition selected from, classified in class 514, subclass 169 for example.

III. Claims 4-6, 10, and 11 drawn to pharmaceutical compositions and a kit comprising specific components herein, classified in class 514, subclass 169 for example.

Inventions Group III; and I-II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, for example, salmon calcitonin may be used in the treatment of osteoporosis.

Each above product and method of treatment relates to a separate and distinct area of pharmaceutical technology. The search for all inventions would place an undue burden on the Office in view of the diversity of the medical disorders to be treated and the corresponding diversity in the field of search for each.